REMARKS

Claims 31-44, and withdrawn method claims 9-12, will be pending in this application after entry of the foregoing amendments. Claim 31 is the only pending independent claim and is a generic claim. Withdrawn claims 9-12 cover a reasonable number of species within the scope of claim 31 and their consideration is respectfully requested upon an indication of allowability of generic claim 1. Claims 1-8 and 13-19 had been cancelled previously, without prejudice. Withdrawn composition claims 20-30 have been cancelled herein without prejudice to their inclusion in a related application.

Claim 31 has been amended merely to include in the preamble an antecedent basis for the later recitation of treatment of alopecia in "the" mammal. Clearly the claim is not being narrowed and no new matter is being added by this amendment. Entry of the amendment is respectfully solicited.

In the outstanding Office Action, comprising a final rejection, the Examiner rejected claims 31-37 under 35 U.S.C. § 103(a) as being unpatentable over Drug Launches (June 6, 1988) and rejected claims 38-44 under 35 U.S.C. § 103(a) as being unpatentable over Drug Launches further in view of Lurie U.S. Patent 6,075,005 ("Lurie"), both for the reasons previously mentioned in an Office Action mailed June 3, 2004.

In the final rejection, the Examiner took the position that chlorhexidine, a bisbiguanide compound, is not structurally distinguishable from biguanide compounds that are characterized as insulin sensitivity increasing substances (ISISes), and therefore, the characterization of a compound as an ISIS in claims 31-37 are not distinguishable from "the same (biguanide) compound utilized for the same effect (treatment of alopecia) taught by the prior art."

In the final rejection, the Examiner also took the position that it would have been obvious to one of ordinary skill in the art to combine a steroid enzyme inhibitor or inducer (STI) as claimed in claims 39, 43 and 44 and/or an androgen receptor blocking agent (ARB) claimed in claims 40-44, with the biguanide compound taught by Drug Launches because "all of the components are well known individually effective for the treatment of alopecia" and, as such, "it would be expected that the combination of all of the components would treat alopecia as well."

Applicants respectfully, but strenuously, traverse the rejections for the reasons set forth below and as supported by the accompanying Declaration Under 37 C.F.R. § 1.132 of Rozlyn A. Krajcik, Ph.D., R.Ph. (the "Krajcik Declaration"), and its attached Exhibits.

Dr. Krajcik is a named co-inventor and co-applicant of the above-identified application, and Assistant Director – Scientific Affairs and Director of Laboratories at the Orentreich Foundation for

the Advancement of Science, Inc., the assignee of the present invention and application (Krajcik Declaration paragraph 2). Her primary research focus is on the impact of endocrinological disorders on skin health and hair growth, as well as 13 years as a Managing Registered Pharmacist and other education and experience as shown in her curriculum vitae attached as Exhibit A to the Krajcik Declaration. This background leads to her consideration by herself and others as an expect in the subject matter of this application and one who has worked with and is familiar with those who are persons of ordinary skill in the art of this application, namely, people with advanced degrees in life sciences and several years of experience (Krajcik Declaration paragraphs 2 and 3). As noted both in the claims and in paragraph 5 of the Krajcik Declaration, the focus of the present application is on the use of an ISIS to treat mammalian alopecia. This is a new use for an ISIS which, as claimed in claim 31, is administered to the mammal in a manner so as to reach an affected area of a pilosebaceous apparatus. As such, the identification of the active ingredient in the claimed method of a material or substance as an ISIS is important, regardless of the structure of the particular ISIS used. As indicated in claim 34, the ISIS could be a biguanide, or as indicated in withdrawn claims 9 and 12, the ISIS could also be a thiazolidinedione or a D-chiro-inositol, for instance. The important discovery and basis for the present invention is the new use of an ISIS administered to a mammal so as to reach an affected area of a pilosebaceous apparatus.

Where structure becomes important is where the structure makes it apparent that a material or substance, even one which the Examiner characterized as a biguanide, such as chlorhexidine (more appropriately characterized as a bisbiguanide – see Krajcik Declaration paragraph 7 and Exhibit B) does not have a function of an ISIS. In the present case, it is clear that chlorhexidine is not an ISIS and that not all biguanide compounds would be ISISes (Krajcik Declaration paragraph 11).

More specifically, chlorhexidine is a "bisbiguanide with bacteriostatic activity," and is characterized for human and veterinary therapeutic uses as an 'antiseptic; disinfectant'" (Krajcik Declaration paragraph 7 and Exhibit B). Chlorhexidine's antiseptic or disinfectant antimicrobial function is based on its chlorinated phenyl rings, part of a structure which is considerably different from the structure of metformin, the exemplary biguanide compound mentioned throughout the application and its examples, having a structure shown in Exhibit C (Krajcik Declaration paragraph 7).

Other information relating to chlorhexidine, such as the printout of the online entry in Thomson's Micromedex catalog attached as Exhibit D to the Krajcik Declaration, also indicates an antibacterial use for chlorhexidine. In this case, the indications are various treatments for gingivitis, mouth infections, stomatitis and dental plaque. Based on the characteristics of Exhibit D, it is clear

that chlorhexidine is distinguished significantly from metformin and other such small-molecule biguanides, which are readily absorbed from the gastrointestinal tract and penetrate the skin for delivery to a pilosebaceous apparatus as claimed in claim 31. In contrast, as noted in Exhibit D, chlorhexidine is not readily absorbed from the gastrointestinal tract, nor would it penetrate the skin (Krajcik Declaration paragraph 8). A literature review failed to locate any evidence that chlorhexidine is or would be considered to be an ISIS. The contrary appears to be true. The literature suggests that if chlorhexidine were to be delivered to the cells comprising hair follicles, it would interfere with glycolysis, a metabolic activity stimulated by insulin and required for energy production in hair follicles. Thus, this one aspect of many involved in insulin activity, namely stimulation of glycolysis, is not a function or characteristic of chlorhexidine. The interference is believed to be caused by a membrane-damaging effect of chlorhexidine. See Krajcik Declaration paragraph 9 and Exhibits E and F.

Additional supporting evidence demonstrates that chlorhexidine interferes with sugar transport and metabolism, hardly characteristics of an ISIS. See Krajcik Declaration paragraph 10 and Exhibits G, H and I.

Although Drug Launches asserts that the composition stimulates hair growth and prevents hair loss, there is no indication whatsoever in the mere listing of ingredients and statement of use that the Novian Forte product announced by Drug Launches is an ISIS or that any of its ingredients would be considered an ISIS (Krajcik Declaration paragraph 12). Thus, just because a product claims to stimulate hair growth or prevent hair loss does not mean it is an ISIS.

Moreover, although the Examiner has referred several times to the commercial availability of Novian Forte, it is noted that the June 1988 issue of Drug Launches cited by the Examiner identifies the manufacturer as Pacific Ph located in Korea. To the extent that the Examiner is relying upon commercial availability, the Examiner has not presented any evidence of commercial availability of Novian Forte in the United States. Thus, commercial activity in a foreign country would not qualify Novian Forte as prior art available under 35 U.S.C. § 103(a) via 35 U.S.C. § 102(a) or (b). Moreover, a search by the undersigned attorney on September 28, 2005, using the Google® and Yahoo® search engines for "Novian Forte," "novian forte," "Novian and Forte," and "novian and forte" revealed no relevant information concerning the asserted product in Drug Launches.

In view of the fact that chlorhexidine is not an ISIS and could not function as an ISIS, and is not believed in any way to have any function in treating alopecia, let alone increasing the sensitivity of insulin, reconsideration and withdrawal of the rejections of claims 31-37 based only on Drug Launches are respectfully solicited.

At the very least, in view of the very significant differences between chlorhexidine and metformin, claim 35 directed to the use of metformin, should be allowable.

Since the primary reference fails to provide a basis for an obviousness determination, an obviousness determination based on a combination of Drug Launches and Lurie must also fall, even assuming only for the sake of argument that it would be proper to combine Drug Launches and Lurie.

Applicants further traverse the combination rejection of claims 38-44 over *Drug Launches* in view of Lurie, even assuming only for the sake of argument that Lurie adequately discloses compounds that could be considered to be an STI or an ARB, on the grounds that nothing would suggest, either in Drug Launches or in Lurie, the combination of any of them with an ISIS. Nor is there any disclosure that any asserted STI or ARB of Lurie would enhance the function, effectiveness or administration of an ISIS. Therefore, based both on the lack of an appropriate disclosure in Drug Launches and the failure of even a combination of Drug Launches with Lurie to suggest the invention claimed in claims 38-44, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

Also enclosed is a Second Supplemental Information Disclosure Statement, together with the references cited in the corresponding European patent application. Applicants have received a Communication Under Rule 51(4) EPC by which the European Patent Office (EPO) indicated its intention to grant a European patent based on the application. The Examiner's consideration and acknowledgment of the references in the Second Supplemental Information Disclosure Statement are respectfully solicited.

For the Examiner's information and consideration in reviewing the newly cited references, Applicants provide the following explanation of the important distinctions between myo-inositol disclosed in the references, which is not an ISIS, compared to D-chiro-inositol, referred to in the present application, which is an ISIS.

The only inositol compound mentioned in the present application as being an ISIS compound, and the only inositol compound mentioned in any way in the present application, is D-chiro-inositol (see page 2, line 26; page 5, lines 8-11; page 6, lines 21-23 and 29-30; page 7, lines 30-32; claim 12; canceled claim 25; and the Abstract at page 22, lines 1-2). None of the prior art references cited by the EPO mentions D-chiro-inositol.

As stated at the bottom of page 3 of D3 (WO 95/05146), inositol is a constituent of all animal and vegetable cells. Its chemical formula is identical to that of simple sugars ($C_6H_{12}O_6$), but the atoms are disposed in a different manner. There are nine isomeric forms of inositol, but most of the inositol found in nature is myo-inositol, which is an isomer having vitamin activity (see the attached

monograph 5001 from *The Merck Index*, Thirteenth Edition 2001). In contrast, D-chiro-inositol, which is an ISIS, must be specially extracted or synthesized. Applicants are aware of no teaching in the prior art that myo-inositol is an ISIS, and in fact, myo-inisotol given as an oral supplement does not have the insulin sensitizing effects of D-chiro-inositol.

Therefore, a person skilled in the art would understand the inositol used in the inventions of each of the three references D3 to D5 (identified at Sheet 1 of the EPO Communication enclosed with the accompanying IDS) to be the common form of inositol found in nature, namely myo-inositol, not the particular form of inositol which is an ISIS and which is used in the invention of the present application, namely D-chiro-inositol. Moreover, the person skilled in the art would not find any teaching of the use of an ISIS from any of the three prior art references D3 to D5.

D3 (WO 95/05146) discloses hair loss compositions for oral administration containing at least one of inositol and other constituents. Hair loss may occur from many causes, but D3 does not mention alopecia, to which the present invention is directed. Moreover, as noted above, D3 does not disclose D-chiro-inositol or the use of an ISIS. Instead, in view of the other purpose of the invention of D3, namely treating brittle nails, it is obvious to one skilled in the art that the use of inositol in D3 is in the nature of a vitamin treatment. This is the function of the commonly used inositol, namely myo-inositol. Accordingly, one skilled in the art would not believe that D3 is using D-chiro-inositol or any other ISIS to treat alopecia.

D4 (U.S. Patent 5,043,162) discloses a combination of lower alkyl nicotinate and histamine hydrochloride for stimulating and increasing hair growth and lessening or preventing hair loss (see column 2, lines 8-12, and column 1, lines 48-55). Inositol is listed as an ingredient in the formulations of this patent (see Table 1), but there is no disclosure of the function of inositol in these compositions. Certainly, there is no disclosure that inositol is an active ingredient in promoting hair growth or lessening hair loss. Instead, it appears that inositol is merely one of the adjuvants referred to in the patent. In any event, as noted above, there is no disclosure in this patent of D-chiro-inositol or the use of an ISIS to treat alopecia.

D5 (FR-M-3203) discloses an antiseptic composition, notably for the treatment of infections of the scalp. The composition contains various ingredients for various purposes. The ingredient responsible for acting against functional problems of the scalp and against alopecia is pantothenic acid, which is also said to accelerate pigmentation of the hair. Pantothenic acid is said to cooperate with active ingredients such as inositol and vitamin B6 (see page 1, right column, second full paragraph), but it is not stated what activity inositol has. In any event, there is no mention of D-chiro-inositol, no mention of ISIS, and inositol is only present in the composition in an amount of

0.01%. Therefore, one skilled in the art would not gain any teaching from D5 that would suggest the use of an ISIS, such as D-chiro-inositol, for the manufacture of a medicament for the treatment of alopecia.

In view of the foregoing explanation, it should be apparent, as recognized by the EPO, that the references cited by the EPO do not render the present invention unpatentable.

Reconsideration and withdrawal of all of the rejections and an early Notice of Allowance of all pending claims are respectfully solicited.

Kristyne Bullock, formerly the corresponding attorney handling this application, is no longer with Applicants' law firm identified below. Accordingly, please communicate further with the undersigned attorney, who would be pleased to discuss this case with the Examiner to advance the prosecution of the application.

Respectfully submitted,
ROZLYN A. KRAJCIK, *et al.*

Sept. 29, 2005 By: _____
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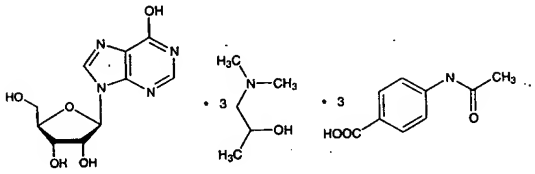
ASN/hg

$[\alpha]_D^{18}$ −49.2° (c = 0.9 in H_2O). $[\alpha]_{white}^{20}$ −73° (0.5 g + 2 ml *N* NaOH + 3 ml H_2O). 100 ml of the satd water soln at 20° contain 1.6 g inosine. Absorption spectrum: Kalckar, *loc. cit.* uv max (pH 6.0): 248.5 nm (ε 12200). Boiling with 0.1*N* H_2SO_4 yields hypoxanthin and D-ribose.

THERAP CAT: Activates cellular functions.

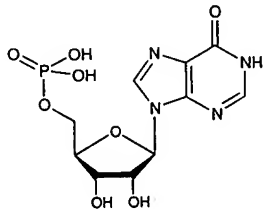
4999. Inosine Pranobex. [36703-88-5] Inosine mono[4-(acetylamino)benzoate] (salt) compd with 1-(dimethylamino)-2-propanol (1:3); inosine:dimethylaminoisopropanol acetamidobenzoate (1:3); inosiplex; methisoprinol; NP-113; NPT-10381; Aviral; Delimmun; Imunoviral; Isoprinosin; Isoprinosina; Isoprinosine; Isoviral; Modimmunal; Pranosina; Pranosine; Viruxan. $C_{52}H_{78}N_{10}O_{17}$; mol wt 1115.23. C 56.00%, H 7.05%, N 12.56%, O 24.39%. Immunostimulant complex formed from the *p*-acetamidobenzoate salt of dimethylaminoisopropanol and inosine in a 3:1 molar ratio. Prepn: P. Gordon, **DE 1965431**; *idem*, **US 3646007** (1971, 1972 both to Newport Pharm.). Antiviral activity: E. R. Brown, P. Gordon, *Can. J. Microbiol.* **18,** 1463 (1972); R. L. Muldoon *et al., Antimicrob. Ag. Chemother.* **2,** 224 (1972). Stimulatory effect on T-cell function: L. Binderup, *Int. J. Immunopharmacol.* **7,** 93 (1985). Pharmacology and therapeutic potential: D. M. Campoli-Richards *et al., Drugs* **32,** 383 (1986). Clinical immunopharmacology: A. J. Glasky, J. F. Gordon, *Cancer Detect. Prev. Suppl.* **1,** 597 (1987). Clinical trial in subacute sclerosing panencephalitis (SSPE): C. E. Jones *et al., Lancet* **1,** 1034 (1982); G. Gascon *et al., Brain Devel.* **15,** 346 (1993). Clinical trial in pre-AIDS patients: C. Pedersen *et al., N. Engl. J. Med.* **322,** 1757 (1990). Review of efficacy in HIV infection: C. De Simone *et al., Int. J. Immunopharmacol.* **13,** Suppl. 1, 19-27 (1991).



Neutral water-soluble solid. LD_{50} in mice and rats (mg/kg): >4000 orally and i.p. (Gordon).

THERAP CAT: Immunomodulator; antiviral.

5000. Inosinic Acid. [131-99-7] 5′-Inosinic acid; 5-inosinic acid; muscle inosinic acid; t-inosinic acid; hypoxanthine riboside-5-phosphoric acid; IMP. $C_{10}H_{13}N_4O_8P$; mol wt 348.21. C 34.49%, H 3.76%, N 16.09%, O 36.76%, P 8.90%. Prepn from meat extract: Levene, Bass, *Nucleic Acids* (New York, 1931) p 229; from dried sardines: Yoshida, Kageyama, **JP 56 732** (1956 to Ajinomoto), *C.A.* **51,** 3870b (1957). Structure: Levene, Bass, *op. cit.*, pp 187-192; Bredereck, *Ber.* **66,** 198 (1933); Levene, Tipson, *J. Biol. Chem.* **111,** 313 (1935). Also prepd from muscle by enzymatic deamination of muscle adenylic acid: Ostern, *Biochem. Z.* **254,** 65 (1932); by hydrolysis of inosine triphosphate: Kleinzeller, *Biochem. J.* **36,** 729 (1942). Studies on the enzymatic synthesis: Greenberg, *J. Biol. Chem.* **190,** 611 (1951); Korn *et al., ibid.* **217,** 875 (1955). Microbial fermentation method using mutant strains of *Micrococcus glutamicus:* Kinoshita *et al.,* **US 3232844** (1966 to Kyowa).



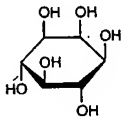
Syrup, solidifies to a glass when dried over H_2SO_4. Agreeable sour taste. pK_1 = 2.4; pK_2 = 6.4. Absorption spectrum: Kalckar, *J. Biol. Chem.* **167,** 445 (1947). Freely sol in water, in formic acid; very sparingly sol in alcohol, ether. On boiling with acid hydrolyzes to 1 mol H_3PO_4, 1 mol hypoxanthine, 1 mol D-ribose.

Disodium salt dihydrate. $C_{10}H_{11}N_4Na_2O_8P.2H_2O$. Barely sol in alcohol, ether, acetone; soly in water at 20° about 13 g/100 ml. Kawasaki, *New Food Ind. (Tokyo)* **3,** no. 1, 17 (1961).

Barium salt. $C_{10}H_{11}BaN_4O_8P$. Hemipentadecahydrate, lustrous leaflets. Becomes anhydr at 100° *in vacuo.* $[\alpha]_D^{20}$ −18.5° (0.3 g of anhydr Ba salt in 10 ml of 2.5% HCl).

USE: Its salts as flavor intensifiers, like sodium glutamate. Examples of mixtures of sodium inosinate and sodium glutamate or other salts: Toi *et al.,* **US 3109741** (1963 to Ajinomoto).

5001. Inositol. [87-89-8] *myo*-Inositol; *meso*-inositol; *i*-inositol; hexahydroxycyclohexane; cyclohexanehexol; cyclohexitol; meat sugar; inosite; mesoinosite; phaseomannite; dambose; nucite; bios I; rat antispectacled eye factor; mouse antialopecia factor. $C_6H_{12}O_6$; mol wt 180.16. C 40.00%, H 6.71%, O 53.28%. Widely distributed in plants and animals. Growth factor for animals and microorganisms. Isoln from heart muscle: Scherer, *Ann.* **73,** 322 (1850); from liver: Woolley, *J. Biol. Chem.* **139,** 29 (1941). Synthesis: Wieland, Wishart, *Ber.* **47,** 2082 (1914); Anderson, Wallis, *J. Am. Chem. Soc.* **70,** 2931 (1948). Obtained commercially from corn steep liquor, since inositol is present as phytic acid in corn: Bartow, Walker, *Ind. Eng. Chem.* **30,** 300 (1938); **US 2112553** (1938); Hoglan, Bartow, *J. Am. Chem. Soc.* **62,** 2397 (1940); Elkin, Meadows, **US 2414365** (1947); **GB 601273** (1948 to Corn Prod. Refining). Nine possible stereoisomers: Seven are optically inactive or *meso.* Two optically active forms, the racemic form, and several *cis,trans*-isomers occur naturally. The prevalent natural form is *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol which is described here. *Reviews:* R. Beckmann, *m-Inosit* (Editio Cantor, Aulendorf, 1953); several authors in *The Vitamins,* **vol. 2,** W. H. Sebrell, Jr., R. S. Harris, Eds. (Academic Press, New York, 1954) pp 321-386; *ibid.* **vol. 3** (2nd ed., 1971) pp 340-415.



Anhydr, non-hygroscopic crystals from water or acetic acid above 80°. Sweet taste. d 1.752. mp 225-227°. Optically inactive. Soly in water at 25°: 14 g/100 ml soln; at 60°: 28 g/100 ml soln. Slightly sol in alc. Practically insol in ether and other common organic solvents. Aq solns are neutral to litmus.

Dihydrate. Efflorescent crystals from water below 50°. d 1.524. mp 218°. Becomes anhydr at 100°.

Monophosphate. [573-35-3] $C_6H_{13}O_9P$. Prepn: Posternak, Posternak, *Helv. Chim. Acta* **12,** 1165 (1929); McCormick, Carter, *Biochem. Prepn.* **2,** 65 (1952). Crystals from water + alcohol, dec 195-197°. Titrates as a dibasic acid. Freely soluble in water (1 g dissolves in 3 ml H_2O). Practically insol in abs ethanol, ether. Remarkably resistant to hydrolysis by boiling with strong alkali. May be hydrolyzed by boiling with 6*N* HCl for 14 hrs.

THERAP CAT: Vitamin B complex; lipotropic.

5002. Inositol Niacinate. [6556-11-2] *myo*-Inositol hexa-3-pyridinecarboxylate; hexanicotinoyl inositol; hexanicotinyl *cis*-1,2,3,5-*trans*-4,6-cyclohexane; inositol hexanicotinate; *meso*-inositol hexanicotinate; Dilcit; Dilexpal; Mesotal; Esantene; Hämovannid; Hexanicit; Hexopal; Linodil; Mesonex; Palohex. $C_{42}H_{30}N_6O_{12}$; mol wt 810.72. C 62.22%, H 3.73%, N 10.37%, O 23.68%. Prepn: Badgett, Woodward, *J. Am. Chem. Soc.* **69,** 2907 (1947).